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*RESEARCH ARTICLE*

# PAEDIATRIC ACUTE MYELOID LEUKAEMIA; CLINICAL CHARACTERISTICS AND TREATMENT OUTCOME; EXPERIENCE FROM A DEVELOPING COUNTRY.

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## Abstract

**Objective**: To document the demographics and treatment outcome of Paediatric Acute Myeloid Leukaemia (AML) at a tertiary care facility of Pakistan.

**Methods**: The prospective descriptive study conducted at the Paediatric Oncology department, Combined Military Hospital (CMH) Rawalpindi, Pakistan. All newly registered cases of AML under eighteen years of age from 1st January 2012 onwards who completed their treatment before 30th September 2018 were included.

**Results**: Data of 187 cases of De novo AML, including 117 (62.6 %) males and 70 (37.4 %) females was analysed. The mean age was 6.1 ± 3.53 years. The most common presenting features were pallor 156 (83.4%), fever 143 (76.5%) & bruising/bleeding 95 (50.8 %). Sixty-six (35.3 %) patients had WBC >50x$10^9$/L at presentation. The most common FAB subtype was M-2 in 85 (45.5 %), followed by M-4 in 25 (13.4 %) cases. The overall treatment related mortality (TRM) was 55/187 (29.4%). The major causes of TRM were neutropenic sepsis and bleeding. Sixty patients had refractory or relapsed disease and 53 (88.3%) of them also died. Total 121 patients completed full treatment. OS and DFS of these 121 patients were 65.3 % and 59.5% respectively.

**Conclusions:** This is the largest study of Paediatric AML from Pakistan. High TRM, primarily during induction chemotherapy and relapsed/refractory disease are the major causes of treatment failure. AML-M2 has the best survival rates. Malnutrition, high WBC counts at presentation and unfavourable cytogenetics have decreased OS and DFS rates. Use of Etoposide during induction chemotherapy does not give any survival advantage.



## Introduction:

Acute myeloid leukaemia (AML) in children is rare, accounting for 15–25% of childhood leukaemia with a yearly incidence rate of 5–7/million. In high-income countries, five years survival rates of paediatric AML now approaches 70 % due to recent advances in chemotherapy, risk based intensive treatment and better supportive care.(1-3) However, most children live in low-income countries (LICs), where survival is still very low. The contributing

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factors to this survival differences are; delay in diagnosis, abandonment of therapy, co morbid conditions including malnutrition, suboptimal supportive careand higher treatment related mortality (TRM)(4-6).

Because of limited treatment facilities, poor socioeconomic conditions and unaffordability of treatment, high TRM and high relapse rate, majority of children with AML are not treated in Pakistan. Very limited published data is available on presentation and outcomeof childhood AML from this part of the world. The majority ofpublished data focuses on morphology and refers to bothadults and children.(5) Paediatric Oncology department at Combined Military Hospital Rawalpindi is the only centre in Pakistan, which is treating all types of paediatric AML coming from all over the country. This study describes the clinical characteristics and treatment outcome of childhood AML in Pakistan.

**Patients and Methods**

This is a prospective on-going study being carried out at Paediatric Oncology department at Combined Military Hospital (CMH) and Armed Forces Bone Marrow Transplant Centre (AFBMTC) Rawalpindi, Pakistan. CMH and AFBMTC are military hospitals primarily responsible for treating army personnel and their dependents. However, because of the scarcity of dedicated facilities for haematology and oncology in the country, a large number of civilians especially from the northern Pakistan are also treated here. The hospital ethical committee approved the study and informed consent was obtained from parents of the patients. Data collection was started in January 2012. Study data included: age, sex, blood counts at presentation, central nervous system (CNS) status, French American-British (FAB) classification, immunophenotype, genetic abnormalities at diagnosis, chemotherapy protocol, treatment outcome, use of HSCT, last follow up, and cause of death if applicable.

The study included all newly diagnosed patients of de novo AML younger than 18 years of age who were registered from 1st January 2012 and completed their treatment before 30th September 2018. Patients having Acute Promyelocytic Leukaemia (APL), prior chemotherapy or leaving during treatment were excluded from the study.

Detailed medical history and clinical examination was performed on each case. All the patients were weighed at the time of admission before start of the chemotherapy. The weight was recorded in kilograms and plotted on the standard WHO Z-score chart for age and sex. The patients were categorized as adequately nourished, moderately malnourished and severely malnourished if they had Z score >-2, between ≤-2 to >-3 and ≤-3 respectively. Diagnosis of AML was made on bone marrow morphology and flow cytometric immunophenotyping by standard techniques. Initial work up included full blood count, coagulation profile, and biochemical profile including hepatic and renal function tests, and cardiac function assessment by performing echocardiography.

**Therapy**

Treatment was based on AML17 Paediatric version.

**Induction therapy;**

Two courses of Anthracycline based chemotherapy either ADE (Daunorubicin 50 mg/m$^2$ daily on days 1, 3 & 5, Cytarabine 100 mg/m$^2$ 12-hourly on days 1-10 and Etoposide 100 mg/m$^2$ daily on days 1-5) or AD (Daunorubicin 50 mg/m$^2$ daily on days 1, 3 & 5 and Cytarabine100 mg/m$^2$ 12-hourly on days 1-10) were used as induction chemotherapy course 1. Second induction chemotherapy was same as chemotherapy course 2, but Cytarabine was given for 8 days.

**Post-remission therapy;**

Two courses of high dose Cytarabine based chemotherapy (HiDAC; Cytarabine 3000 mg/m$^2$ twice daily on day 1, 3 and 5) were used as consolidation therapy. Patients showing partial response after induction chemotherapy received FLA-Ida (Fludarabine 30 mg/m$^2$ daily on days 1-5, Cytosine Arabinoside 2000 mg/m$^2$ dailyon days 1-5 and Idarubicin 10 mg/m$^2$ on days 4, 5 & 6) as consolidation therapy.

**Haematopoietic Stem cell transplantation;**

Patients with high-risk disease, having HLA matched sibling donor available, underwent allogeneic stem cell transplantation (SCT). The conditioning regimen used consisted of Busulfan, Cyclophosphamide, and Melphalan (BuCyMel) with Methotrexate and Cyclosporine for graft-versus-host disease (GVHD) prophylaxis.

**Supportive Care;**

All patients were hospitalized for the initiation of induction chemotherapy. Tumour lysis prophylaxis with hyper-hydration and allopurinol was commenced 24 hours prior to the start of chemotherapy and continued for at least 4

days. Rasburicase and leukapheresis were not used for any case. Intake, output and electrolytes were monitored carefully.

Subsequent chemotherapy was given as inpatient or in day care as outdoor cases. Outdoor cases were admitted immediately in case of fever or any other problem. Patients not admitted in the hospital were reviewed at least twice weekly in outdoor clinics. No prophylactic antimicrobials and colony stimulating factors were used during neutropenic period. However, all cases of febrile neutropenia were treated as inpatient with broad-spectrum intravenous antibiotics. Fever was defined as a single oral temperature of >38°C or two readings > 37.5°C at least 2 hours apart. Neutropenia was defined as absolute neutrophil count (ANC) of < 1000. Febrile patients with ANC < 1000 were treated with a combination of Pipracillin-Tazobactam and Amikacin. Vancomycin or Teicoplanin were added if central venous line infection was suspected. Pipracillin-Tazobactam was swapped with Meropenam if fever continued after 48 hours. Anti-fungal Amphotericin B was added empirically if fever continued beyond 96 hours.

Blood and blood products transfusion was given on regular basis. Haemoglobin transfusion threshold was 8.0 gm/dL. Thresholds for Platelet transfusion were $10x10^9$/L for asymptomatic patients, and $20x10^9$/L for febrile patients.

**Definitions**

The **diagnosis** of AML was based upon morphological analysis of bone marrow (BM) aspirates according to the FAB classifications.

**Complete Remission (CR)** was defined as <5% blasts in the BM; absence of blasts with Auer rods; absence of extramedullary disease; absolute neutrophil count >1x $10^9$/l; platelet count >100 x $10^9$/l; independence of red cell transfusions

**CR with incomplete recovery (CRi);** All Complete Remission criteria except for residual neutropenia (ANC < $1.0x10^9$/l) or thrombocytopenia (<100 $x10^9$/l)

**Partial Remission (PR)**; All haematological criteria of CR; decrease of BM blast percentage to 5–25%; & decrease of pre- treatment bone marrow blast percentage by at least 50%.

**Resistant/Refractory Disease (RD)**; Failure to achieve CR or CRi; only includes patients surviving ≥7 d following completion of initial treatment, withevidence of persistent leukaemia by blood and/or bone marrow examination. **RD** was defined as >5% blasts in the BM after two courses of induction treatment.

**Early Death** was defined as death before or at treatment day 42.

**Death in Aplasia;** Death occurring ≥7 day following completion of initial treatment while cytopenic; with an aplastic or hypoplastic bone marrow obtained within 7 day of death, without evidence of persistent leukaemia

**Death from indeterminate cause**; Death occurring before completion of therapy, or <7 day following its completion; or deaths occurring ≥7 day following completion of initial therapy with no blasts in the blood, but no bone marrow examination available

**Relapse;** Bone marrow blasts ≥ 5%; or reappearance of blasts in the blood; or development of extra-medullary disease after attaining CR.

**Statistical analysis**

Survival analyses were performed using the Kaplan-Meier method in SPSS 25. Chi-square test was applied, and frequencies and percentages calculated. Disease-free survival (DFS) was defined as the time from achievement of CR until relapse. Overall survival (OS) was defined as the time from the date of diagnosis till last follow-up or death from any cause (OS). Log rank tests were used to compare survival differences. $P \leq 0.05$ was considered statistically significant.

## Results:-

During the study periodtotal 241 new patients of Acute Myeloid Leukaemia were registered at the Paediatric oncology department of Combined Military Hospital Rawalpindi. Fifty-four cases including 39 cases of APL, six cases, which died before start of chemotherapy, three casesthat refused treatment and six cases, which were still on treatment at the time of analysis, were excluded from the study.

**Patient Characteristics**

Data of 187 cases of De novo AML was analysed. Only 27 (14.4%) patients were children of army personnel. There were 117 (62.6%) males and 70 (37.4%) females. Age at diagnosis ranged from nine months to 15 years with the mean 6.1 ± 3.53 years. The mean duration of symptoms before reporting to oncologist was 54.54 days with a range from 1 to 425 days.

The most common presenting feature was pallor in 156 (83.4 %) followed by fever in 143 (76.5%) and bruising/bleeding in 95 (50.8 %). Physical examination revealed pallor in 156 (83.4%) patients followed by visceromegaly in 141 (75.4%) patients. Unilateral or bilateral proptosis was seen in 28 (15%) cases. The mean white blood cells count was 53.68±67.95x$10^9$/l and ranged from 1.1 to 408 x$10^9$/l. Initial WBC of > 50x$10^9$/L was seen in 66 (35.3 %) patients. The mean haemoglobin was 7.5±2.49 g/dl, and the mean platelets count was 55.71±80.86x$10^9$/l.

Only 6 (3.2 %) patients had CNS (central nervous system) disease. The most common FAB subtype was M-2 in 85 (45.5%), followed by M-4 in 25 (13.4 %) cases. Results of genetic analysis were available in 99 (52.9%) cases. The majority of cases 48/99 (48.5%) had normal cytogenetics followed by 34/99 (34.3%) favourable and 14/99 (14.1%) unfavourable abnormalities (Table 1).

**Treatment and outcome analysis**

Out of 187 cases, 112 (59.9 %) patients had ADE chemotherapy and 75 (40.1 %) had D3A10 chemotherapy. The results of 1st chemotherapy were; death 42 (22.5%) cases, morphological remission 110 (58.8%) cases, partial response 23 (12.3%) and refractory disease 12 (6.4%) cases. Second course of chemotherapy was given to 142 cases. After two courses of induction chemotherapy treatment out come was; TRM 50/187 (26.7%), CR 119/187 (63.6%), PR 11/187 (5.9%) and RD 4/187 (2.1%). Overall (OS) was 67.6%, 43.8%, and 28.6% in favourable, intermediate and unfavourable cytogenetic risk group respectively (p=0.042). Where as, DFS was 62.2%, 41.7%, and 28.6% in favourable, intermediate and unfavourable cytogenetic risk group respectively (p=0.057). Total 121/187(64.7%) cases completed full treatment. OS and DFS of 121 patients who completed treatment was 65.3 % and 59.5% respectively.

We also looked at various factors influencing the OS and DFS and found that nutritional status, AML subtypes, Cytogenetics and WBC counts at presentation had statistically significant impact on treatment outcome. (Table 2 and figures 1, 2 and 3)

**Mortality**

In the present cohort overall, non-relapse mortality (NRM) was 55/187 (29.4%) including 42/187 (22.5%), 8/142 (5.6%) and 5/129 (3.9%) during 1st, 2nd and 3rd chemotherapycourses respectively. No patient died during the 4thcourse of chemotherapy. The major causes ofNRM were neutropenic sepsis and bleeding. Sixty cases had refractory or relapsed disease and 53/60 (88.3%) also died. Thus, the overall mortality was 108/187 (57.7%).

## Discussion:

This study of 187 patients represents the largest cohort of children with AML studied in Pakistan. The clinical presentation of AML is diverse and depends on leukaemic infiltration of bone marrow and other organs. The major presenting symptoms in the present study were: fever, pallor, and bleeding/bruises.

Myeloid sarcoma (MS), or chloroma, is an extra-medullary tumour mass composed of malignant myeloid precursor cells (8). MS occurs in bone marrow and spreads via Haversian canals to penetrate periosteum and form a soft-tissue mass.Most frequently involved sites are bone, skin, or lymph node, although any part of the body may be affected.(9) The presentation depends upon the size and location of the tumour (10). MS has been reported in 2.5–8.0% of patients with AML and occurs concurrently with or at relapse of bone marrow leukaemia (11). In the present study, 30 (16.0%) cases presented with MS manifesting mainly as proptosis. Although with chemotherapy proptosis resolved, however, five patients (16.7%) lost vision in one eye because of exposure keratitis and destruction of eye due to ocular MS. Two patients presented with difficulty in walking due to spinal cord compression, which also resolved after induction chemotherapy. Sixteen (53.3%) cases of MS were associated with AML-M2. Isolated MS without any evidence of leukaemia in the peripheral blood and bone marrow is rare. In the present study, 2 (1.1%) patients presented with isolated primary MS (BM examination showed <5 % blasts). One patient presented with proptosis only while the other had proptosis and spinal cord compression resulting in difficulty in walking. Both cases of isolated MS were treated with systemic chemotherapy as AML. Lee JY et al reported incidence of MS as1.8 % in 497 cases of AML (8).

Higher WBC count at presentation is a poor prognostic factor and is associated with lower CR rate and worse OS. (12)We documented the same finding. In the present study, CR rates after two courses of induction chemotherapy were 54.2 % and 28.9% (p=0.007) in patients having WBC less than and more than $50x10^9$/l respectively. OS and DFS were also statistically significantly better in patients with WBC count less than $50x10^9$/l. OS was 47.9 % and 31.8 % (p=0.044) and DFS was 44.6 % and 27.3% (p=0.013) in groups having WBC less than $50x10^9$/l and more than $50x10^9$/L respectively. This finding of better CR, OS and DFS with low WBC at presentation is similar to the results of Medical Research Council AML12 trial in children with AML(12).

Central nervous system (CNS) involvement at diagnosis in paediatric AML has an incidence of 6–29% (3). It is more common in AML-M4 subtype. CNS involvement at diagnosis was documented in 6 (3.2%) patients in our study. Fadoo at el (5) reported CNS disease in 5 (13%) cases and another study from Saudi Arabia reported CNS disease in 31 (17.7%) cases (13). This difference in CNS presentation may be related to underlying FAB subtype as Fadooet al reported more cases of AML-M4 in their study.

AML with maturation (AML-M2) is the most common subtype of AML in children (14). Same finding was documented in the present study. The most common FAB subtype was AML-M2 followed by AML-M4. Similar frequency is reported by other studies.(12-14)However, Fadoo et al from Pakistan reported AML-M4 as the commonest FAB subtype (5).AML-M2 is associated with favourable cytogenetics and better OS and DFS. The best OS and DFS were observed in AML-M2 in the present study. OS and DFS was 54.0 % and 50.6 % in AML-M2. (Figure 1 a and b; OS and DFS according to FAB AML subtypes)

AML develops as the consequence of a series of genetic changes in a haematopoietic precursor cell and specific cytogenetic abnormalities have considerable prognostic significance and affect the treatment planning. AML can be stratified into favourable, intermediate, and adverse risk based on cytogenetic and molecular profiles. Presence of certain chromosomal rearrangements, such as t(8;21), t(15;17), or inv(16), confer a more favourable prognosis, whereas presence of other cytogenetic profiles, such as complex karyotypic changes, monosomy 5 and 7 are associated with less-favourable prognosis. AML with normal cytogenetics typically constitutes an intermediate prognostic risk, and accounts for approximately 50% of AML cases (15). In the present study, results of genetic analysis were available in 99/187 (52.9%). Some patients came with the diagnosis of AML and samples for cytogenetics were not taken, as family was not willing to repeat bone marrow sample. In few cases cytogenetics culture failure lead to inconclusive results. Cytogenetic abnormalities had prognostic significance and statistically significant difference between different cytogenetic risk groups were documented in the present study. OS was 67.6%, 43.8%, and 28.6% (p=0.042) in favourable, intermediate and unfavourable cytogenetic risk groups respectively. Where as, DFS was 62.2 %, 41.7%, and 28.6% (p=0.057) in favourable, intermediate and unfavourable cytogenetic risk group respectively. (Figure 2 a and b; OS and DFS according to cytogenetic risk groups)

An unhealthy body mass index (BMI) is associated with worse survival and high TRM in children with AML (16). In the present study, 71 (38.0%) were malnourished and OS and DFS were significantly low in malnourished children than in well-nourished children. OS was 48.3 %, 40.5 % & 20.7 % (p=0.004) and DFS was 44.0 %, 35.7% and 20.7 % (p=0.025) in well nourished, moderately malnourished and severely malnourished children, respectively. (Figure 3 a and b; OS and DFS according nutritional status)

Addition of Etoposide to the induction therapy has failed to show any advantage in adult AML. (17)In the present study, Etoposide was removed from induction chemotherapy with an idea to decrease treatment related complications and mortality. OS and DFS were better in the group receiving induction chemotherapy without Etoposide (log rank P=0.325). OS was 35.5 % and 56.7 % and DFS was 32.7% and 52.2 % and in groups with and without Etoposide (log rank P=0.313). (Figure 4 a and b; OS and DFS according use of Etoposide)

Mortality, either treatment related mortality (TRM) orrelapse related mortality (RRT) remains a majorcause of reduced OS and DFS in AML. Despite the availability of excellent supportive care, TRM remains an important problem for children with AML in high-income countries (HICs), where rates of 7.6–13.8% have been reported (4, 18-20). However, due to unavailability of very robust supportive care support and intensive care support in low-income countries (LICs), TRM rate is much high. In the present cohort TRM was 55/187 (29.4%) and majority of patient, 50/55 (90.9%) died during induction chemotherapy, including 42/187 (22.5%) and 8/142 (5.6%) during 1$^{st}$, 2$^{nd}$ chemotherapy courses respectively. Only 5/129(3.9%) died during consolidation phase (3$^{rd}$ chemotherapy course). No patient died during the 4$^{th}$ course of chemotherapy. The major causes of TRM were neutropenic sepsis

and bleeding. Gupta S et al has reported very similar results from a study conducted in El Salvador, Guatemala and Honduras (4). Fadoo et al from Pakistan reported TRM of 17.4 % in a small study of 23 cases only (5).

**Table 1:-**Patient characteristics

| | **Number (n)** | **Percentage (%)** |
|---|---|---|
| **Total number** | **187** | **100** |
| **Age** | Mean 6.1 ± 3.53 years (Range; 9 months to 15 years) | |
| Less than 5 years | 75 | 40.1 |
| >5-10 years | 77 | 41.2 |
| >10-15 years | 35 | 18.7 |
| **Sex** | | |
| Male | 117 | 62.6 |
| Female | 70 | 37.4 |
| **Duration of symptoms** | Mean 54.54 days (Range; 1-425 days) | |
| **Presentation** | | |
| • Pallor | 156 | 83.4 |
| • Fever | 143 | 76.5 |
| • Visceromegaly | 141 | 75.4 |
| • Bruising & Bleeding | 95 | 50.8 |
| • Bone Pains | 28 | 15.0 |
| • Proptosis | 28 | 15.0 |
| • CNS Positive | 6 | 3.2 |
| • Granulocytic Sarcoma | 2 | 1.1 |
| • WBC count ($x10^9$/L) | Mean 53.68 (Range; 1.1-408) | |
| o (< 50 $x10^9$/L) | 121 | 64.7 |
| o (> 50 $x10^9$/L) | 66 | 35.3 |
| • Haemoglobin (g/dl) | Mean 7.56 (Range; 2.9-15.9) | |
| • Platelets ($x10^9$/L) | Mean 55.7 (Range; 2-684) | |
| **FAB Classification** | | |
| • AML-M0 | 14 | 7.5 |
| • AML-M1 | 21 | 11.2 |
| • AML-M2 | 85 | 45.5 |
| • AML-M4 | 25 | 13.4 |
| • AML-M5 | 9 | 4.8 |
| • AML-M6 | 4 | 2.1 |
| • AML-M7 | 4 | 2.1 |
| • Granulocytic Sarcoma | 2 | 1.1 |
| • AML-DS | 3 | 1.6 |
| • AML-NOS | 20 | 10.7 |
| **Cytogenetic Analysis** | **99** | **52.9** |
| • **Normal Cytogenetics** | **48** | **48.5** |
| • **Favourable** | **34** | **34.3** |
| o AML1-ETO | 26 | 26.3 |
| o CBFB-MYH11 | 7 | 7.0 |
| o NPM1 Mutation | 1 | 1.0 |
| • **Unfavourable** | **14** | **14.1** |
| o Complex Cytogenetics | 12 | 12.1 |
| o FUS-ERG | 1 | 1.0 |
| o Monosomy 7 | 1 | 1.0 |
| • **Trisomy 21** | **3** | **3.0** |

Relapsed or refractory disease is the major cause of mortality in AML (4, 5, 21). In the present study, 60/187 (32.0%) had relapsed/ refractory disease and 53 (88.3%) of them died.It has been established that allogeneic stem cell transplant is of benefit for all patients in CR2 (21, 22). Only three patients could undergo allogeneic stem cell transplant in out study, mainly because of very limited facilities available for SCT in our setup. All of them are surviving without any complication. Majority of relapsed/refractory disease died because they were offered only palliative care.

The disease-free survival and overall survival of 121 patients who completed treatment was 59.5 % and 65.3 % respectively. These results should encourage other Paediatric oncology centres in the country to treat paediatric AML. Although this study shows low survival rates as compared to survival data from more developed countries. However, provision of better supportive care and haematopoietic stem cell transplantation (HSCT) facilities can improve the survival rates comparable to those in HICs.

## Conclusion:

This is the largest study of Paediatric AML from Pakistan. High TRM, primarily during induction chemotherapy and relapsed/refractory disease are the major causes of treatment failure. AML-M2 has the best survival rates. Malnutrition, high WBC count at presentation and unfavourable cytogenetics has decreased OS and DFS rates. Use of Etoposide during induction chemotherapy does not give any survival advantage.

**Table 2:** Results of difference in survival times between the groups studied at all time points. Statistical Tests of Association Between OS & DFS and Study Variables in AML Patients

| Variable | OS | | DFS | |
|---|---|---|---|---|
| | *Log Rank* | | *Log Rank* | |
| | *Chi square* | *P* | *Chi square* | *P* |
| Nutritional Status | 11.001 | 0.004 | 7.378 | 0.025 |
| AML Subtype | 21.576 | 0.006 | 19.794 | 0.011 |
| Cytogenetics risk factors | 6.322 | 0.042 | 5.729 | 0.057 |
| WBC at Presentation | 4.070 | 0.044 | 6.207 | 0.013 |
| CNS disease | 1.079 | 0.299 | 0.952 | 0.329 |
| Duration of symptoms before presenting to oncologist | 0.850 | 0.654 | 0.869 | 0.648 |
| Treatment ADE versus D3A10 | 0.967 | 0.325 | 1.016 | 0.313 |

**Figure 1 a and b:**-OS and DFS according to FAB AML subtypes

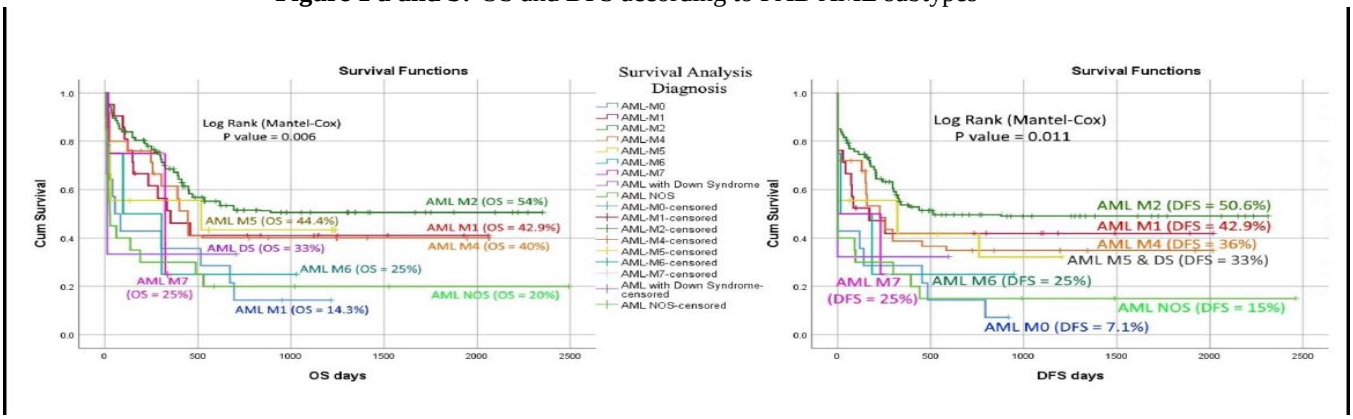


**Figure 2 a and b:**-OS and DFS according to cytogenetic risk groups

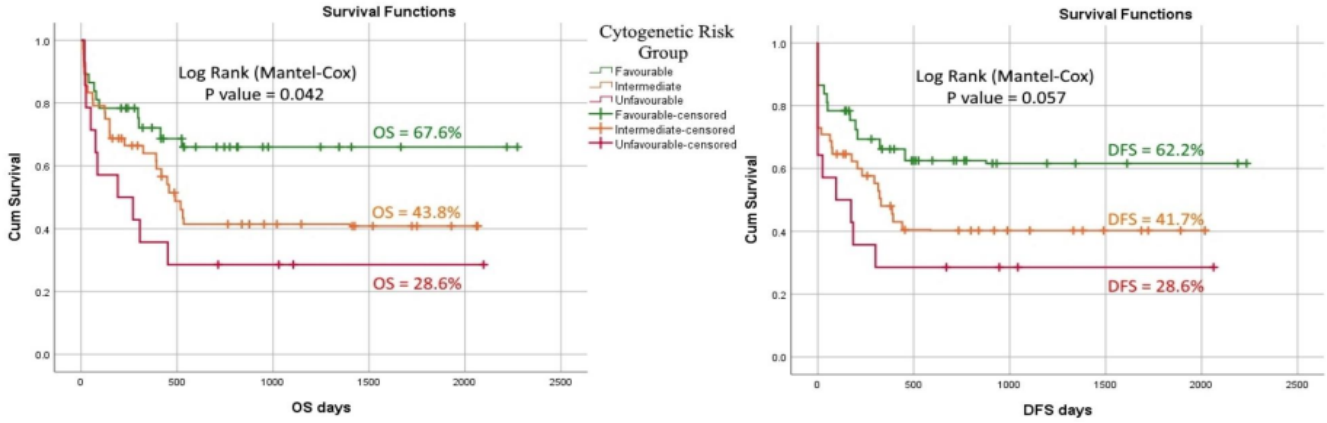



**Figure 3 a and b:**-OS and DFS according nutritional status

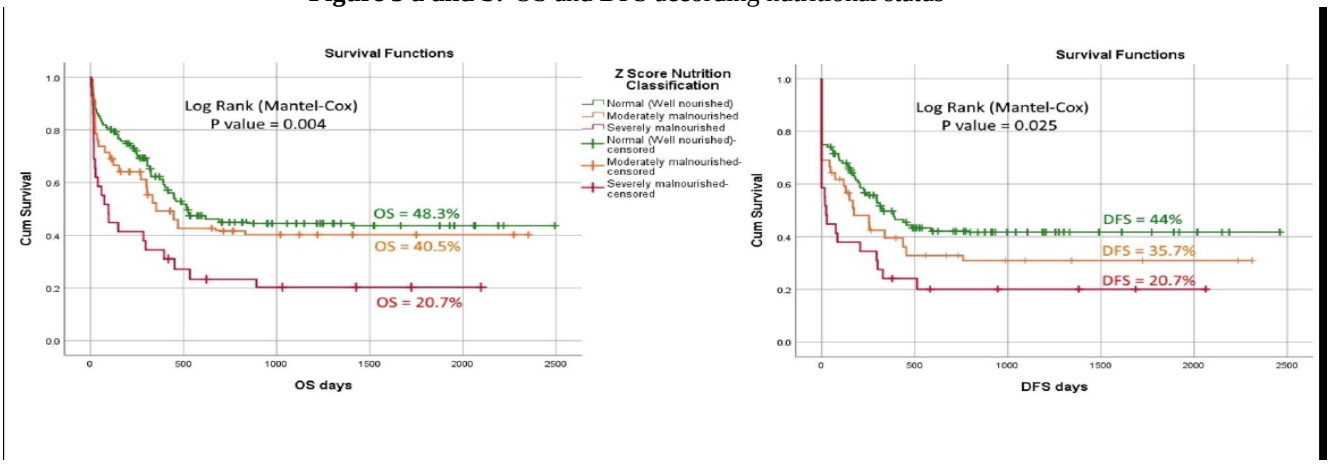
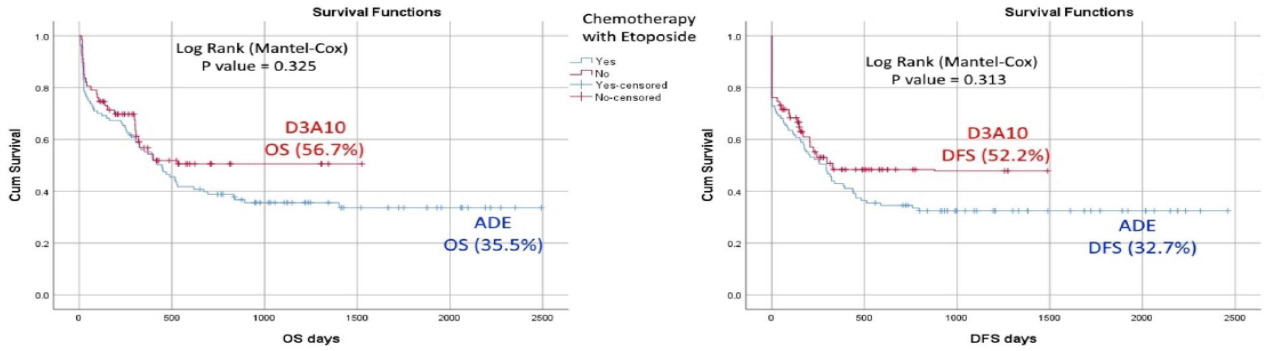



**Figure 4 a and b:**-OS and DFS according use of Etoposide



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